Background

The Cancer Assessment Review Committee (CARC) evaluated the epidemiological and experimental animal studies employing the agency's 2005 Guidelines for Carcinogen Risk Assessment. The cancer guideline emphasizes the importance of a weight of evidence (WOE) approach in reaching conclusions about the human carcinogenic potential of agents. This is accomplished in a single integrative step after assessing all of the individual lines of evidence. Evidence considered includes tumor findings, or lack thereof, in humans and laboratory animals; an agent's chemical and physical properties; its structure-activity relationships (SARs) as compared with other carcinogenic agents; and studies addressing potential carcinogenic processes and mode(s) of action (MOA), either *in vivo* or *in vitro*. Data from epidemiological studies are generally preferred for characterizing human cancer hazard and risk. However, all of the information discussed above could provide valuable insights into the possible mode(s) of action and likelihood of human cancer hazard and risk (USEPA, 2005).

1. **What weight is given to epidemiologic evidence in assigning descriptors for cancer classification**?

"Carcinogenic to Humans"

This descriptor indicates strong evidence of human carcinogenicity. It covers different combinations of evidence.

- This descriptor is appropriate when there is **convincing epidemiologic evidence of a causal association** between human exposure and cancer.
- Exceptionally, this descriptor may be equally appropriate with a lesser weight of epidemiologic evidence that is strengthened by **other lines of evidence**. It can be used when all of the following conditions are met:
  - (a) there is strong evidence of an association between human exposure **and** either cancer or the key precursor events of the agent's mode of action but not enough for a causal association, **and**
  - (b) **there is extensive evidence of carcinogenicity in animals, and**
  - (c) the mode(s) of carcinogenic action and associated key precursor events have been identified in animals, **and**
  - (d) there is strong evidence that the key precursor events that precede the cancer response in animals are anticipated to occur in humans and progress to tumors, based on available biological information.

CARC Assessment: This descriptor/classification is not applicable since the epidemiological evidence at this time does not support a causal relationship between glyphosate exposure and solid tumors, non-solid tumors (leukemia, multiple myeloma or Hodgkin lymphoma) and evidence at this time is inconclusive for a causal or clear associative relationship between glyphosate exposure and non Hodgkins Lymphoma (NHL). Furthermore, there is no evidence of carcinogenicity in animals (4 studies in mice and 7 studies in rats).

"Likely to Be Carcinogenic to Humans"

This descriptor is applicable when the weight of the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor "Carcinogenic to Humans". Supporting data for this descriptor may include:

- an agent demonstrating **a plausible (but not definitively causal**) association between human exposure and cancer, in most cases **with some supporting biological, experimental evidence,** though not necessarily carcinogenicity data from animal experiments;

- an agent that has tested positive in animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans;

- a positive tumor study that raises additional biological concerns beyond that of a statistically significant result**,** for example, a high degree of malignancy, or an early age at onset;

- a rare animal tumor response in a single experiment that is assumed to be relevant to humans; or

- a positive tumor study that is strengthened by other lines of evidence**,** for example, either plausible (but not definitively causal) association between human exposure and cancer or evidence that the agent or an important metabolite causes events generally known to be associated with tumor formation (such as DNA reactivity or effects on cell growth control) likely to be related to the tumor response

CARC Assessment: This descriptor/classification is not applicable based on the following woe considerations:

No statistically significant association or an straight association between glyphosate exposure and NHL was seen in six case-control studies and in the AHS prospective cohort study. Although a plausible (but not definitely causal) association was seen in a case control study from Sweden, there is no biological plausibility for establishing causality. The extensive experimental data (carcinogenicity, genotoxicity and/or mechanistic evidence) does not provide evidences to form a basis for an association between exposure to glyphosate and the development of NHL. In 9 of the 11 carcinogenicity studies no treatment-related neoplasm were identified and in the remaining two studies there was no consistent pattern of neoplasm formation demonstrating that the effect is not reproducible and therefore not treatment-related.

There is no evidence of carcinogenicity when tested in two strains of rats in 7 studies. Tumors were seen in one sex (male), one species (mice) and one strain (CD-1). Of the four carcinogenicity studies in mice, kidney tumors were seen in males in one study and hemangiosarcomas were seen in males in another study. The increase in these tumors, however, did not reach statistical significance in a pair-wise comparison with the concurrent controls. The presence of these tumors did not raise a biological concern since there were no pre-neoplastic lesions for the kidney tumors; there was no high degree of malignancy or early onset of these tumors; hemangiosarcomas are commonly seen in this strain of mice; and, the tumors were seen only at the limit dose or at 5-fold higher than the limit dose (kidney tumors at 5000 mg/kg/day and hemangiosarcomas at 1000 mg/kg/day). Additionally, if really treatment-related, it is unlikely that the same tumors would not

have been replicated in the other three studies in the same strain of mice.

"Suggestive Evidence of Carcinogenic Potential"

This descriptor of the database is appropriate when the weight of evidence is suggestive of carcinogenicity; a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion. This descriptor covers a spectrum of evidence associated with varying levels of concern for carcinogenicity, ranging from a positive cancer result in the only study on an agent to a single positive cancer result in an extensive database that includes negative studies in other species. Depending on the extent of the database, additional studies may or may not provide further insights. Some examples include:

- a small, and possibly not statistically significant, increase in tumor incidence observed in a single animal or human study that does not reach the weight of evidence for the descriptor "Likely to Be Carcinogenic to Humans." The study generally would not be contradicted by other studies of equal quality in the same population group or experimental system;

- a small increase in a tumor with a high background rate in that sex and strain, when there is some but insufficient evidence that the observed tumors may be due to intrinsic factors that cause background tumors and not due to the agent being assessed. (When there is a high background rate of a specific tumor in animals of a particular sex and strain, then there may be biological factors operating independently of the agent being assessed that could be responsible for the development of the observed tumors.) In this case, the reasons for determining that the tumors are not due to the agent are explained;

- evidence of a positive response in a study whose power, design, or conduct limits the ability to draw a confident conclusion (but does not make the study fatally flawed), but where the carcinogenic potential is strengthened by other lines of evidence (such as structure-activity relationships); or

- a statistically significant increase at one dose only, but no significant response at the other doses and no overall trend.

CARC Assessment: This descriptor/classification is not applicable based on the following woe considerations:

Although the concern for potential carcinogenic effects in humans is raised, the totally of data from the epidemiological studies are judged not sufficient for a stronger conclusion.

The weight of evidence from the carcinogenicity studies in mice and rats did not reach the level of evidence need for a "likely" classification. The presence of kidney tumors in male mice in one study was contradicted by the lack of formation of this tumors in the other three studies of equal quality in the same strain of mice. Similarly, the increased incidence of hemangiosarcomas observed in male mice in one study may be due to an inherent increase in the background incidences and really not due to treatment since this tumor type was not seen in the other three studies in the same sex and strain of mice when tested at comparable or even at high doses (4000 mg/kg/day).

There was no structure-activity relationship to strengthen the carcinogenic potential since no evidence of carcinogenicity was seen in mice or rats administered sulfosate (the trimethylsulfonium salt of glyphosate) for two years.

"Not Likely to Be Carcinogenic to Humans"

This descriptor is appropriate when the available data are considered robust for deciding that there is no basis for human hazard concern. In some instances, there can be positive results in experimental animals when there is strong, consistent evidence that each mode of action in experimental animals does not operate in humans. In other cases, there can be convincing evidence in both humans and animals that the agent is not carcinogenic. The judgment may be based on data such as:

- animal evidence that demonstrates lack of carcinogenic effect in both sexes in well-designed and well-conducted studies in at least two appropriate animal species (in the absence of other animal or human data suggesting a potential for cancer effects),
- convincing and extensive experimental evidence showing that the only carcinogenic effects observed in animals are not relevant to humans,
- convincing evidence that carcinogenic effects are not likely by a particular exposure route, or
- convincing evidence that carcinogenic effects are not likely below a defined dose range.

CARC Assessment: This descriptor/classification is applicable based on the following woe considerations:

Overall evidence from epidemiological studies are inconclusive for a causal associative relationship between glyphosate exposure and cancer in human studies. There is no evidence to support a causal relationship between glyphosate exposure and solid tumors and non-solid tumors (leukemia, multiple myeloma, or Hodgkin lymphoma). The evidence at this time is inconclusive for a causal or clear associative relationship between glyphosate and NHL. Multiple case-control studies and one prospective cohort study found no association; whereas, results from a small number of case-control studies (mostly in Sweden) did suggest an association. Limitations for most of these studies include small sample size, limited power, risk ratios with large confidence intervals, and recall bias as well as missing data. The literature will continue to be monitored for studies related to glyphosate and risk of NHL.

In experimental animals, there were no statistically significant increase in the occurrence of any tumor type in mice (4 studies) or rats (7 studies). The small increased incidences of kidney tumors in male mice in one study and hemangiosarcomas in male mice in a another study were determined to be not treatment-related due to the lack of: pre-neoplastic changes; statistical significance in pair-wise comparison tests; consistency in multiple studies; and were within the historical control range. Furthermore, the lack of a dose-response across several orders of magnitude in multiple studies suggests that no individual tumor of single etiology is attributed to treatment. Thus, these factors minimizes the statistical significance seen in trend tests (but not in pair-wise) comparison) *per se.* A wide range of assays both *in vitro* and *in vivo* including endpoints for gene mutation, chromosomal damage, DNA damage and repair, there is no *in vivo* genotoxic or mutagenic concern for glyphosate.